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Art Unit : 1625
Examiner : B. M. ROBINSON

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.132

I, Pierre LESTAGE, a citizen of France, 9, Allée de la Grande Terre, 78170 La Celle St Cloud, France, declare and say that :

I hold the degree of Doctor in Philosophy in Neurosciences from the University of Lyon I, France, in 1987.

Since November 1987 I have been working in SERVIER :

- From November 1987 to December 1994 : I had a Senior Research position and I was responsible for the development of *in vivo* behavioral models as part of a screening program for the discovery of novel cognition enhancers and/or neuroprotective drugs towards acute and chronic neurodegenerative diseases.

- From January 1995 to September 1998 : I was Research Project Leader in the field of neuropharmacology. I was responsible for various research projects aimed to the discovery of novel cognition enhancers and/or neuroprotective drugs.

- From October 1998 to December 1999 : I was director of the department of Neurobiology at Servier, responsible for all the *in vivo* preclinical experiments performed in the field of neuropharmacology for the discovery of novel cognition enhancers and neuroprotective drugs.

- From January 2000-present : I am Director of the Division of Cerebral Pathology at Servier. The main topic of research of this division is the discovery of novel cognition enhancers and neuroprotective drugs against pathological cerebral aging, acute and chronic neurodegenerative diseases.

I am the author or co-author of 31 patents and 40 international publications, the majority of which are devoted to Neuropharmacology.

I am one of the co-inventors of US Patent Application Serial n° 09/888,990 filed June 20, 2001 concerning "1,1- and 1,2-disubstituted cyclopropane compounds ".

I am thoroughly familiar with the above-mentioned patent application and fully support the pharmacological experiments contained therein which were performed either by me or under my supervision. I also fully support the conclusions derived and the arguments presented as concerns the therapeutic interest of the compounds described.

The compounds of the present invention exhibiting specific interaction with nicotinic receptors of type $\alpha 4\beta 2$, they will be used in the treatment of neuropathologies associated with cerebral ageing, mood disorders, pain and tobacco withdrawal.

The compounds disclosed in the present application (US Serial n° 09/888,990) are potent and selective $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChRs) ligands and have potent *in vivo* effects of acetylcholine release in the rat prefrontal cortex and are able to increase mnesic retention and decrease algia.

This is illustrated by various binding tests following the procedures described in the application US Serial n° 09/888,990 page 55, line 9 to page 57, line 30.

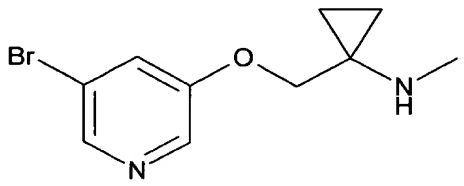
Results

Table 1 – Displacement of binding of [^{3}H]-cytisine on "type α4β2" nicotinic receptors of rat brain

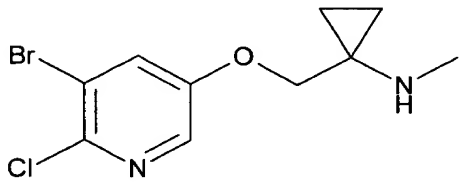
Compounds	***Ki (nM)***
Example 18	3.0
Example 19	44.0
Example 22	12.4
Example 23	12.2
Example 24	7.14
Example A	10.9
Example B	5.5

Examples A and B are compounds of the invention not specifically described in the Specification. These compounds are included in this declaration to further illustrate the Y radical of the compounds of the invention.

Example A :



Example B :



The results of the tests described in examples 38 to 41 in the application US Serial n° 09/888,990 page 55 line 9 to page 57 line 12, show that, up to a concentration of 10μM, all the above mentioned compounds have a Ki>10000 nM.

Table 1 shows clearly that compounds of the invention have a strong affinity for central nicotinic receptors of type $\alpha 4\beta 2$. The other tests which were performed on those compounds show that they have no significant affinity for nicotinic receptors of the "muscular $(\alpha 1)2\beta\delta\gamma$" type, for nicotinic receptors of the "ganglionic $\alpha 3\beta 4$" type, for muscarinic M_2-M_4 receptors and for type $\alpha 7$ central nicotinic receptors.

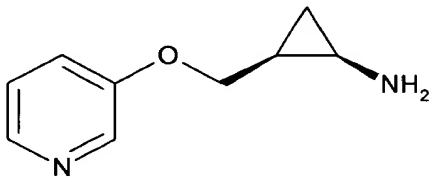
Table 2 – *In vivo measurement of the release of acetylcholine by means of intra-cortical microdialysis in the conscious Wistar rat*

Compounds	**AUC[a] (ACh) Prefontal Cortex***
Example 18	13938
Example 19	11955
Example 23	7966.5
Example A	8751.5
Example C	14333

[a] Area Under Curve ; * 3 mg/kg i.p.

Example C is a compound of the invention not specifically described in the Specification. This compounds is included in this declaration to further illustrate the 1,2 substitution on the cyclopropyl ring of the compounds of the invention.

Example C :



The results disclosed in Table 2 show that the compounds of the present invention increase, the cortical release of acetylcholine in a dose-dependant manner for a dose of 3 mg/kg i.p. indicating the $\alpha 4\beta 2$-agonist character.

Table 3 – *Abdominal contractions induced by phenyl-p-benzoquinone (PBQ) in the NMRI mouse*

Compounds	**% Inhibiti n PBQ cramps (mg/kg i.p.)**
Example 14	-52 (10) -87 (20)
Example 18	-83 (3)
Example 19	-76 (3) -92 (10)
Example 23	-52 (10) -90 (30)
Example 24	-80 (3)

The results disclosed in Table 3 show inhibition ranging from 52 to 92 % for doses ranging from 3 to 30 mg/kg i.p. for the compounds of the invention indicating that they possess antalgic properties.

Table 4 – *Social recognition in the Wistar rat*

Compounds	**Minimal active dose (mg/kg i.p.)**
Example 14	1.0
Example 18	0.30
Example 19	1.0
Example 22	3.0
Example 24	1.0
Example A	1.0

The results disclosed in Table 4 show the memorization properties of the compounds of the invention.

We have demonstrated that representative compounds of US Serial n° 09/888,990 have a high affinity for nicotinic receptors of the type $\alpha 4\beta 2$ receptors, that they present an $\alpha 4\beta 2$-agonist character and possess antalgic properties and enhance memorization.

The therapeutic properties of nicotine and other nicotinic agents are based upon activity with respect to central receptors, which differ structurally and pharmacologically from peripheral receptors. The central receptors of type $\alpha4\beta2$ are the most represented in the central nervous system and have been implicated in the majority of the therapeutic effects of nicotine. The following publications, submitted with this Declaration correlate and demonstrate the relationship between $\alpha4\beta2$ nicotinic acetylcholine receptors and the various diseases claimed to be treatable in the present invention.

A number of reviews on compounds acting at nicotinic acetylcholine receptors (nAChRs) have been published (Neuropsychopharmacology, 2000, 22, 451-465 ; Cur. Med. Chemistry, 2001, 8, 651-674 ; Jpn. J. Pharmacol., 2002, 88, 133-138 ; J. Pharm. Exp. Ther., 2000, 292, 461-467). Nicotine and nicotinic ligands which are mainly compounds acting on the $\alpha4\beta2$ nAChRs show promise for novel treatments for a variety of diseases such as age-related cognitive disorders and Alzheimer's disease (Psychopharmacology, 1998, 138, 217-230 ; Psychopharmacology 1999, 143, 158-165 ; Dementia, 1996, 7, 47-52), Schizophrenia (Am. J. Psychiatry, 1993, 150, 1856-1861 ; Biol. Psychiatry, 1992, 32, 607-616 ; Biol. Psychiatry, 1998, 44, 98-106), Attention-deficit/hyperactivity disorder (Psychopharmacology, 1996, 123, 55-63), Depression (Neuroreport, 1998, 9, 57-60), Tourette's syndrome (Drug Dev. Res., 1996, 38, 290-298), Analgesia (Brain Res. Bull., 2002, 57, 133-150), Smoking cessation (J. Pharm. Exp. Ther., 2000, 295, 321-327), Neurodegeneration and Anxiety (Neuropsychopharmacology, 2000, 22, 451-465 ; Jpn. J. Pharmacol., 2002, 88, 133-138).

In conclusion, taking the pharmacological data and the publications into account one skilled in the art would conclude that compounds of the present invention may be used in treatment where specific ligand of $\alpha4\beta2$ receptors is involved and have utility in the treatment of deficiencies of memory associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and subcortical dementias, and also for the treatment of mood disorders, Tourette's syndrome, hyperactivity syndrome with attention-deficit, tobacco withdrawal and pain.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of the title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not

Pierre LESTAGE

Executed at : Courbevoie

Date : December, 4, 2002

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